(k) $-CO_2R^4$;

n is: 0 to 5;

t is: 0, 1 or 2;

R^4 is: H, or (C_1-C_8)-alkyl;

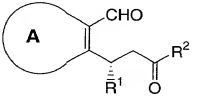
R^5 is: H, (C_1-C_8)-alkyl or aryl, wherein aryl as defined above;

R^6 is: H, (C_1-C_8)-alkyl or aryl, wherein aryl as defined above; and

R^7 is: H, (C_1-C_8)-alkyl, aryl or alkyl, wherein aryl is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, (C_3-C_8)-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$, or when two R^7 substituents are on the same nitrogen they can join to form a ring of 3 to 6 atoms;

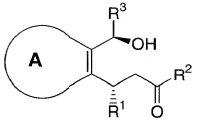
comprising the steps of:

(1) reacting a Grignard reagent with a conjugate adduct compound of Formula II,



II

in the presence of a first aprotic solvent and optionally an additive at a temperature range of about -80°C to about 30°C to give a Grignard addition product of Formula III; and



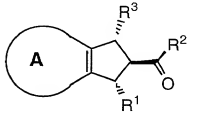
III

(2) adding phosphoramide reagent to a mixture of the Grignard addition product of Formula III, a second aprotic solvent and a base at a temperature range of about -80°C to about 30°C to produce the desired compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a novel way to synthesize the compound for the endothelin receptor antagonist involving a Grignard addition and a cyclization to give a desired compound of endothelin receptor antagonist.

The present invention discloses a process for preparing a compound of Formula I,



I

wherein:

represents:

(a) 5- or 6-membered heterocyclyl containing one to three double bonds, but at least one double bond and 1 to 3 heteroatoms selected from O, N and S, and the heterocyclyl is optionally substituted with one to three substituents

selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, (C_3-C_8)-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$;

(b) 5- or 6-membered carbocyclyl containing one or two double bonds, but at least one double bond, and the carbocyclyl is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, (C_3-C_8)-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$; or

(c) aryl, wherein aryl is defined as phenyl or naphthyl, which is optionally substituted with one to three substituents selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $N(R^5)_2$, (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, (C_3-C_8)-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$, or when aryl is substituted on adjacent carbons they can form a 5- or 6-membered fused ring having one to three heteroatoms selected from O, N, and S, this ring being optionally substituted on carbon or nitrogen with one to three substituents selected from the group consisting of: H, OH, CO_2R^6, Br, Cl, F, I, CF_3, $N(R^7)_2$, (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, (C_3-C_8)-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$;

and wherein (C_1-C_8)-alkoxy, (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, or (C_3-C_8)-cycloalkyl substituent of aryl is further optionally substituted with one to three substituents
selected from the group consisting of: OH, CO_2R^4, Br, Cl, F, I, CF_3, $OCPh_3$, $N(R^5)_2$, (C_1-C_8)-alkoxy, (C_3-C_8)-cycloalkyl, $CO(CH_2)_nCH_3$, and $CO(CH_2)_nCH_2N(R^5)_2$;

R^1 is:

(a) (C_1-C_8)-alkyl, (C_2-C_8)-alkenyl, (C_2-C_8)-alkynyl, or (C_3-C_8)-cycloalkyl,

(b) aryl, wherein aryl as defined above, or

(c) heteroaryl, wherein heteroaryl is defined as a 5- or 6-membered aromatic ring containing one to three heteroatoms selected from O, N and S, and is optionally substituted with one to three substituents